Addressing Concerns with Forensic STR Markers and Genetic Disease Linkage

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International Symposium on Human Identification
October 8, 2013 (Atlanta, GA)

Presentation Outline

- Concerns that have been raised and brief review of the literature
- Forensic STR marker characteristics
- Genetic disease studies (alleles within families) vs. forensic analysis (alleles across populations)
- Impact of STR mutation rates

This Concern is Not New…

Kimpton, C.P., et al. (1995). Report on the second EDNAP collaborative STR exercise. *Forensic Science International*, 71, 137-152.

"…it is likely that many or possibly most STRs will eventually be shown to be useful in following a genetic disease or other genetic trait *within a family* and therefore this possibility must be recognized at the outset of the use of such systems" (emphasis added)

Laird, R., et al. (2007). Forensic STRs as potential disease markers: a study of VWA and von Willebrand's disease. *Forensic Science International: Genetics, 1,* 253-261

Abstract

"In recent years it has been established that non-coding variants may be in linkage disequilibrium (LD) with coding variants up to several thousand base pairs away forming haplotype blocks. These non-coding markers may be haplotype specific and, therefore, informative regarding the surrounding coding sequence. In this study, we chose to study the VWA short tandem repeat (STR) as it is targeted in all major commercial kits utilized in routine forensic DNA profiling and is located in the von Willebrand Factor (vWF) gene; a gene associated with von Willebrand's Disease (vWD)… [T]**here appeared to be no evidence of LD blocks surrounding the VWA STR and evidence for recombination within 3 kb of VWA, hence, it is unlikely that VWA STR alleles could be used to predict haplotypes within the vWF gene that are associated with different forms of vWD.**"

Gil, A., et al. (2013). Linkage between HPRTB STR alleles and Lesch-Nyhan syndrome inside a family: Implications in forensic casework. *Forensic Science International*: *Genetics, 7(1),* e5-e6.

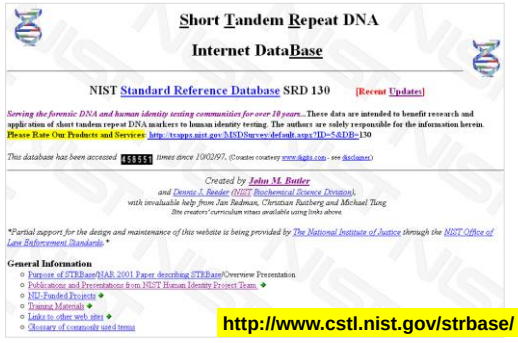
"…In summary, **although located inside a coding gene, HPRTB seems to be safely usable for forensic purposes without revealing any health risks of the subjects**. In the few cases with a known familiar history of LNS or other HPRT1 associated mutations or diseases, in the same way as for other forensic markers that are physically linked to disease-causing mutations, the use of HPRTB for identification purposes should be avoided, or the possibility of inferring genetic risk should be communicated."

Short Tandem Repeat (STR) Markers Used in Forensic DNA Analysis

- Contain mostly tetranucleotide repeat units that are 5-50 repeats in length
- Located within introns or between genes
- Highly variable among individuals
- Multi-allelic to aid mixture detection & interpretation
- Relatively high mutation rate (~0.2% or ~2 in 1000 meioses)

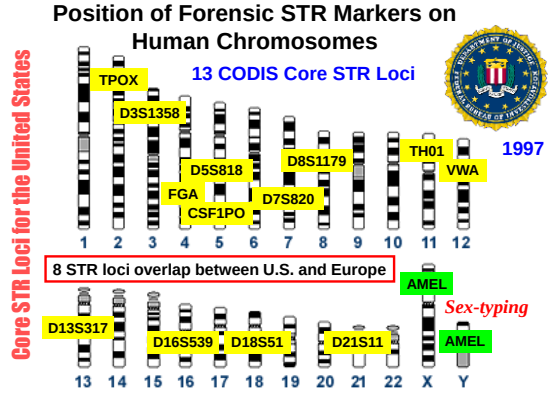
NIST **STRBase** Website

Serving the Forensic DNA Community for >15 Years



http://www.cstl.nist.gov/strbase/

Position of Forensic STR Markers on Human Chromosomes



Expanding the U.S. CODIS Core Loci

D.R. Hares (2012) Expanding the CODIS Core Loci in the United States. *Forensic Sci. Int. Genet.* 6(1): e52-e54
Addendum to expanding the CODIS core loci in the United States, Forensic Sci. Int. Genet. (2012) 6(5): e135

Letter to the Editor

Expanding the CODIS core loci in the United States

CODIS Core Loci Working Group
Formed in May 2010 to make recommendations to FBI CODIS Unit

Douglas Hares (Chair) – FBI
John Butler – NIST
Cecelia Crouse – FL PBSO
Brad Jenkins – VA DFS
Ken Konzak – CA DOJ
Taylor Scott – IL SP

major reasons for expanding the CODIS core loci in the United States:
(1) To reduce the likelihood of adventitious matches [7] as the number of profiles stored at NDIS continues to increase each year (expected to total over 10 million profiles by the time of this publication). There are no signs that this trend will slow down as States expand the coverage of their DNA database programs and increase laboratory efficiency and capacity.
(2) To increase international compatibility to assist law enforcement data sharing efforts.
(3) To increase discrimination power to aid missing persons cases.

Forensic STR loci are not linked to disease…

Katsanis, S.H., & Wagner, J.K. (2013) Characterization of the standard and recommended CODIS markers. *Journal of Forensic Sciences, 58(S1),* S169-S172.

TECHNICAL NOTE
CRIMINALISTICS; JURISPRUDENCE

Sara H. Katsanis,[1] M.S. and Jennifer K. Wagner,[2] J.D., Ph.D.

Characterization of the Standard and Recommended CODIS Markers*

"…we found no documentation of individual genotypes for the 24 STRs [the current and recommended CODIS loci] **to be causative of any documented phenotypes either in the literature or in the interrogated databases."**

See also on http://www.swgdam.org/

Open SWGDAM Letter Regarding the Claims Raised in State v. Abernathy that the CODIS Core Loci are Associated with Medical Conditions/Disease States

"The utility of the CODIS profile … is limited to identification purposes at this time."

"…we can affirm that individual genotypes are not at present revealing information beyond identification."

SWGDAM statement on *Abernathy* ruling

See **http://www.swgdam.org/**

SCIENTIFIC WORKING GROUP — DNA ANALYSIS METHODS

SWGDAM[1] Considerations for Claims that the CODIS Core Loci are 'Associated' with Medical Conditions/Diseases

In a June 2012 ruling, *State v. Abernathy*, No. 3599-9-11, a Vermont Court adopted the testimony from a defense expert on the CODIS core loci and found that "the analogy between DNA testing and fingerprinting is no longer valid, because a DNA profile consisting of the thirteen CODIS loci contains information beyond mere identity." In

http://swgdam.org/SWGDAM%20Abernathy%20Open%20Letter%20APPROVED%2001172013.pdf

From J.M. Butler (2012) *Advanced Topics in Forensic DNA Typing: Methodology*, p. 228

"…[U]se of STRs for family linkage studies is different than associations of specific alleles in a general population with a disease state. Colin Kimpton and coworkers from the European DNA Profiling Group (EDNAP) recognized early on in the application of STRs for human identity testing that 'it is likely that many or possibly most STRs will eventually be shown to be useful in following a genetic disease or other genetic trait *within a family* and therefore this possibility must be recognized at the outset of the use of such systems' (Kimpton et al. 1995; emphasis added). **Family pedigree studies that track a few specific loci and alleles are different than equating a specific allele in the population with some kind of phenotypic correlation**…"

Kimpton, C.P., et al. (1995). Report on the second EDNAP collaborative STR exercise. *Forensic Science International*, 71, 137-152.

From J.M. Butler (2012) *Advanced Topics in Forensic DNA Typing: Methodology*, p. 228

"In 2005, an infrequently used X-chromosome STR marker named HumARA was removed from future consideration in human identity testing (Szibor et al. 2005) since it was located in an exon. Some of the longer CAG repeat alleles with HumARA have been shown to be the cause of a genetic disease, which is why this STR locus was removed from use. **All of the 23 commonly used STR markers described throughout this book and present in current commercial STR kits are located in between genes ('junk DNA' regions) or in introns. Thus, by definition they are non-coding**."

Szibor, R., et al. (2005). Letter to the editor: the HumARA genotype is linked to spinal and bulbar muscular dystrophy and some further disease risks and should no longer be used as a DNA marker for forensic purposes. *International Journal of Legal Medicine*, *119*, 179-180.

From J.M. Butler (2012) *Advanced Topics in Forensic DNA Typing: Methodology*, p. 228

"[T]he relatively high mutation rate of STRs means that even if any linkage existed at one time between a specific allele and a genetic disease state, this linkage would likely not last beyond a few generations before mutation altered the allele length and effectively broke any linkage of an allele or genotype state to that specific phenotype state."

Summary

- STR markers have proven to be valuable in forensic evidence examinations for almost two decades (the U.S. will soon move from 13 to ~20 core STR loci)
- Genetic disease linkage studies often involve STR markers, some of which may be core forensic loci
- The high mutation rate of forensic STR markers means that any potential allele associations with disease phenotypes will not hold over time in the general population

Workshop on October 10, 2013

New Autosomal and Y-STR Loci and Kits: Making Data Driven Decisions

Organizer: John Butler (National Institute of Standards and Technology)

Welcome and Introductory Remarks (John Butler)

NIST Studies: Kit Concordance and U.S. Population Data (Becky Hill)

Experience with PowerPlex Fusion

Experience with GlobalFiler

NIST Studies with New Y-STR Loci & Kits (Mike Coble)

STRBase Resources and Wrap-up (John Butler)

Acknowledgments

Community feedback and contributors to the NIST STRBase website

Office of Special Programs


John Butler

Applied Genetics Group


Pete Vallone


Mike Coble


Becky Hill


Margaret Kline


Erica Butts


Kevin Kiesler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Past and present funding from the **National Institute of Justice**, the **NIST Forensic Science Program** and the **FBI Laboratory** (through the NIST Information Access Division)

Thank you for your attention!

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A copy of this presentation is available at:
http://www.cstl.nist.gov/strbase/NISTpub.htm